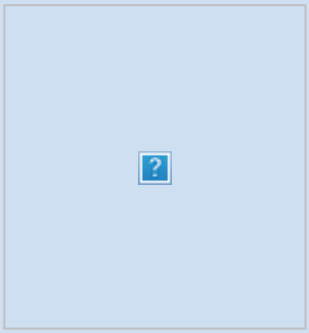
February 2010

Heart Failure: Tracking Patients After Discharge

Heart failure (HF) is one of the leading reasons for hospitalization; however, for a third of patients with HF visiting the emergency department (ED) who are discharged home, little is known about their outcome in comparison to HF patients admitted to the hospital.



"As one of the largest impactors on our healthcare system, it is important to understand what is happening to HF patients when they are not being admitted to the hospital, especially if they risk ending up in the ED again," explains study lead Dr. Douglas Lee.

The TGRI team examined the acute care and early outcomes of more than 50,000 patients with HF who visited an ED and were discharged without hospital admission in Ontario between April 2004 and March 2007. Findings show that approximately 31.7% of patients were discharged without admission to the hospital. Of these discharged patients, 4.0% died within 30 days from admission while 1.3% died within 7 days of discharge from the ED. Interestingly, patients were more likely to be admitted to hospital if they were older, arrived by ambulance or received resuscitation in the ED.

"We discovered that repeat ED visits for HF within 90 days occurred in 20.3% of those initially discharged," says Dr. Lee. "Importantly, recurrent ED visits or hospitalizations after initial discharge increased the risk of death 3.6 times. Our early findings here suggest that there is a definite need for further clinical evidence to guide health care teams in decision-making regarding the safety of direct discharge of patients with HF from the ED."

Lee DS, Schull MJ, Alter DA, Austin PC, Laupacis A, Chong A, Tu JV, Stukel TA. Circ Heart Fail. 2010 Jan 27. [Epub ahead of print]. [Pubmed abstract]. *Research supported by the Ontario Ministry of Health and Long-Term Care, the Canadian Institutes of Health Research, and the Heart and Stroke Foundation of Ontario.*

Leukemia: 'Honing In' on the Genetic Areas of Control

Recent findings from an OCI-led study increase our understanding of the genetics involved in acute myeloid leukemia (AML), a cancer of the blood leading to rapid growth of abnormal white blood cells. These findings may bear important significance in the development of new therapeutic treatments for AML.

The study, carried out by Haytham Khoury in Dr. Mark Minden 's laboratory, used human leukemia cells to conduct a series of genetic tests investigating the *DLK1* gene located on chromosome 14 which in normal cells is expressed only from the chromosome inherited from fathers. In

Mark Your Calendars! Showcasing Krembil Research

Krembil research will be holding its annual Research Day on Wednesday May 12, 2010. The event will take place at 89 Chestnut and will include posters and abstracts from basic and clinical research area.

First the Bad News: CBC Highlights Journey in Cancer Care and Research at PMH

First the Bad News' was an eight-part series broadcast on the Metro Morning radio show hosted by Andy Barrie outlining the cancer journey at the Princess Margaret Hospital (PMH)

The series began on February 1 and featured patient, clinical team and research scientist perspectives on a disease that is still ranked as one of the top killers of Canadians.

To learn more about the series and listen to the interviews visit cbc.ca/Toronto/features/bad-news.

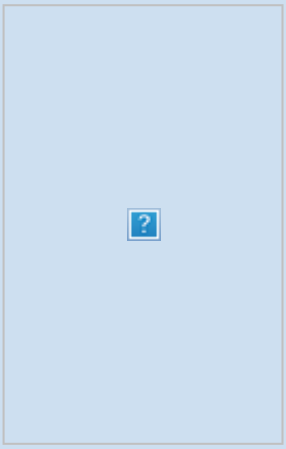
AML approximately 80% of patient cases overexpress DLK1; in some cases this is due to expression from both the paternal and maternal alleles (bi-allelic, or a two-gene, pattern of expression). The activation of the maternal allele is due to hypermethylation—a specific change in *DLK1* gene structure—that results in loss of imprinting or 'gene silencing'. Patients with loss of imprinting have the highest levels of DLK1 RNA and protein.

"In general increased methylation is associated with decreased expression of a gene and this current study has helped to discover that hypermethylation can also serve to turn on genes such as *DLK1*," explains Dr. Minden. "Future work evolving from these studies is aimed at understanding the role of *DLK1* in leukemic blood cell production, and in identifying other genes that may be altered in their expression by gains in methylation at important control points."

Khoury H, Suarez-Saiz F, Wu S, Minden MD. Blood. 2010 Jan 20. [Epub ahead of print]. [Pubmed abstract].

Cancer: Learning the Timing Behind Tumour Development

Findings from the lab of Campbell Family Institute for Breast Cancer Research Director Dr. Tak Mak are helping clarify how the *Lcn2* gene—involved in innate immunity and a number of human cancers—functions during tumour initiation, progression and metastasis in breast and lung cancers.



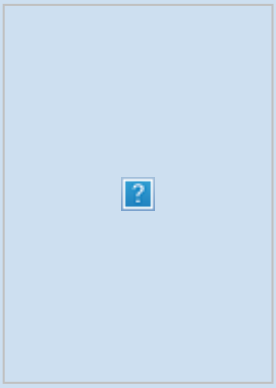
With colleagues, Dr. Mak used a mouse model to monitor the onset and progression of breast tumour development and lung metastasis in females over a 20-week period. Study findings show that mice lacking the *Lcn2* gene experienced a delayed onset of breast tumours as well as significant decreases in multiplicity and tumour burden. Importantly, *Lcn2* was not found to play a role in formation of lung metastases.

Comments Dr. Mak, "We've been able to prove that *Lcn2* plays an important role in the later stages of breast tumour development. Our future studies will continue to investigate if and how *Lcn2* may be suitable as a candidate therapeutic target for breast cancer."

Berger T, Cheung CC, Elia AJ, Mak TW. Proc Natl Acad Sci U S A. 2010 Feb 1. [Epub ahead of print]. [Pubmed abstract]. *Research supported by the Canadian Institutes of Health Research.*

Liver Transplant: Determining When and Why To Apply the Brakes

Living donor liver transplantation (LDLT) is an accepted method used worldwide to treat endstage liver disease. Findings from a TGRI-led study are clarifying the reasons why donor liver surgeries were stopped in the operating room—also known as a 'no go' operation.



"Currently, LDLT comprises less than 5% of adult liver transplant in North America. Encouraging a more widespread use of the procedure will depend on defining optimal recipient and donor characteristics," explains study lead Dr. Ian McGilvray. "It is important to understand why patients who go into the operating room do not donate so that we can improve and further develop this practice."

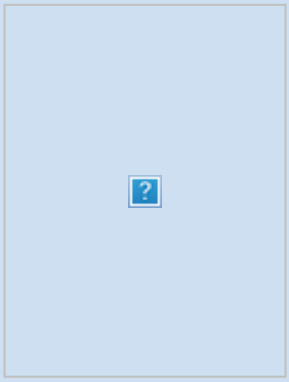
The team conducted a retrospective review of all patients brought to the operating room for donor hepatectomy (right liver lobe removal) between October 2000 and November 2008 and found that out of 257 right lobe donors, the donor operation was aborted in 12 (4.7%) cases. Specifically, operations were aborted due to unusual liver ductal or vascular anatomy, unsuitable liver quality or unexpected intraoperative events that placed donors at unacceptably high risk.

"Understanding elements that prevent surgeries from being completed is an important step in optimizing procedures and most importantly, for maintaining the highest degree of patient safety," comments Dr. McGilvray. "Our findings here have changed our imaging protocol to improve preoperative organ detection and complement our increased appreciation of which cases to avoid based on unique organ structure. With continued improvements to preoperative imaging and assessment criteria, the rate of 'no go' donor liver surgeries should decrease but will never be zero because the unpredictable is always possible."

Guba M, Adcock L, Macleod C, Cattral M, Greig P, Levy G, Grant D, Khalili K, McGilvray ID. Am J Transplant. 2010 Jan 29. [Epub ahead of print]. [Pubmed abstract].

Regenerative Medicine: Repairing the Injured Spinal Cord

Findings from a recent Krembil investigation of spinal cord injuries (SCI) have revealed how to prepare sites of spinal cord damage for cell transplantation, and the particular combination of specific growth proteins promoting function and repair of injured spinal cords. Findings here could bring scientists one step closer to the application of neuronal precursor cell (NPC) or stem cell therapy for these patients.



Led by Krembil's Dr. Michael Fehlings and colleague Dr. Soheila Karimi-Abdolrezaee, the team used an animal model of SCI to show that areas of damage can be primed for cell transplant with the application of chondroitinase ABC (ChABC), which works to keep the area around the scar from negatively influencing the long-term survival and integration of transplanted NPCs. They then went on to show that, when NPCs were injected into the spine with a particular trio of growth proteins, this promoted the integration of NPCs with other spinal cord cells and allowed

the NPCs to mature into oligodendrocytes, a type of nerve cell.

"When we used ChABC to ready the site of damage and then supplemented our NPC transfusion with this particular 'cocktail' of specific growth proteins and applied it to the injured spinal cord, it markedly increased the long-term survival of transplanted cells and greatly optimized their migration and integration in the chronically injured spinal cord," says Dr. Fehlings. "We were also able to show that this particular combination did not enhance the growth of pain nerves in the spine either. We are very excited by these findings because they may facilitate the clinical application of stem cells for patients suffering from chronic SCI."

Karimi-Abdolrezaee S, Eftekharpour E, Wang J, Schut D, Fehlings MG. J Neurosci. 2010 Feb 3;30(5):1657-76. [Pubmed abstract]. *Research supported by the Christopher and Dana Reeve Foundation and the Sam Schmidt Paralysis Foundation, the AOSpine North America, the Canadian Institutes of Health Research, and the Krembil Foundation.*

Rett Syndrome: Brain Activity Patterns Lead to Increased Disease Knowledge

Krembil researchers have discovered how specific gene mutations or genetic changes are involved in the development of Rett Syndrome—an X chromosome-linked genetic disorder primarily affecting girls early in life—which causes previously acquired skills, such as speech and locomotion, to be lost.

"Mice deficient in this gene are instrumental in our efforts to unravel the molecular and cellular events believed to contribute to the deficits seen clinically in girls with Rett syndrome," explains study leads Drs. James Eubanks and Liang Zhang. "We wanted to determine the underlying mechanisms responsible for these altered brain network activities."

With colleagues at the University of Toronto, the team conducted a series of electroencephalography (EEG) investigations—recordings of the electrical activity produced by firing brain cells—to examine brain cell network activity in female and male mice lacking the *Mecp2* gene. Their studies revealed significant decreases in the frequency of hippocampus activity during exploratory behaviours and abnormal rhythmic activity during times when mice were awake but immobile.

"Collectively, our findings show that a deficiency in *Mecp2* gene function in mice leads to alterations in EEG activity compared to mice with the non-mutated MECP2 gene," explains Dr. Eubanks. "While the general activities of these MECP2-deficient networks are largely preserved, alterations are present that may contribute to at least some of the behavioural impairments typically seen in this disease and our findings here could aid in the development of new treatment strategies for Rett syndrome in the future."

D'Cruz JA, Wu C, Zahid T, El-Hayek Y, Zhang L, Eubanks JH. Neurobiol Dis. 2010 Jan 4. [Epub ahead of print]. [Pubmed abstract]. *Research supported by the Canadian Institutes of Health Research, and the Margaret and Howard Gamble Foundation.*

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